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| **APPELLANTS' BRIEF** | Application Number | 09/293,670 |
| | Confirmation Number | 5176 |
| | Attorney Docket No. | RIGL-036CIP |
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| | First Named Inventor | Joseph Fisher |
| | Examiner | Teresa D. Wessendorf |
| Address to:<br>Mail Stop Appeal Brief-Patents<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Group Art | 1639 |
| | Title: MULTIPARAMETER FACS ASSAYS TO DETECT ALTERATIONS IN CELLULAR PARAMETERS AND TO SCREEN SMALL MOLECULE LIBRARIES | |

Sir:

This Brief is filed in support of Appellants' appeal from the Final Rejection dated July 26, 2011. Claims 37-44 are rejected and are appealed herein. A Notice of Appeal was filed on September 23, 2011, making this Brief due by November 23, 2011. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134(a).

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. RIGL-036CIP to cover any required fee for filing the Appellants' brief. Additionally, in the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed account.

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## REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights in the invention to Rigel Pharmaceuticals.

## RELATED APPEALS AND INTERFERENCES

The instant application was appealed in 2008. Appeal No. 2009-015210 is relevant to this case. The Appeal Decision in Appeal No. 2009-015210 is submitted herewith in the Appendix section.

The Board is requested to particularly note that the claims have been substantively revised after appeal.

With reference to prior appeal, the question of whether Uhr discloses a library of *two* retroviral vectors (which was one of the issues argued in the prior appeal) is no longer relevant because that element of the claims has been amended.

With reference to the prior appeal, the question of whether the claims of the instant application are entitled to claim priority to 09/062,330 is still relevant for the rejections over Nolan. This issue is discussed in great detail below.

## STATUS OF CLAIMS (PRESENT CLAIMS STATUS)

Claims 1-36 were canceled.

Claims 37-44 are pending.

Claims 37-44 stand rejected and are appealed herein.

## STATUS OF AMENDMENTS

No amendments to the claims were filed subsequent to issuance of the Final Rejection.

## SUMMARY OF CLAIMED SUBJECT MATTER

Claim 37, the only independent claim, recites a method of screening (page 3, line 36 to page 4, line 5), comprising: introducing a library of at least $10^3$ vectors encoding different candidate agents into a population of mammalian cells grown *in vitro* (page 19, lines 32-34; page 10, lines 8-10; page 19, lines 31-34; page 10, line 20; page 21, lines 1-2 and page 10, lines 10-12); subjecting the population of cells to a physiological signal, wherein the physiological signal stimulates a phenotype in the

cells in the absence of the candidate bioactive agents (page 9, lines 36-37; page 34, line 5); sorting the individual cells in the population on the basis of at least three optical properties by fluorescent activated cell sorting (page 4, line 3); identifying a cell having a phenotype that is altered relative to other cells in the population; and sequencing the nucleic acid encoding said candidate agent in the cell that has an altered phenotype, thereby identifying the candidate agent in the cell (page 28, lines 10-12; page 43, line 20 and page 32, lines 34-36).

Claim 38 requires that the physiological signal is an exocytic inducer, a hormone, an antibody, a peptide, an antigen, a cytokine, a growth factor, an action potential or cells (page 34, lines 5-7; page 20, lines 1-2).

Claim 39 requires that the exocytic inducer is $Ca^{++}$ or ionomycin (page 34, line 6).

Claim 40 requires that the at least three optical properties comprise at least one optical property selected from the group consisting of: light scattering, and fluorescent dye uptake, fluorescent dye release and binding of a fluorescent antibody (page 34, line 37; page 34, line 30 and page 10, lines 35-36).

Claim 41 requires that the library is of at least $10^6$ vectors in size (page 19, line 20).

Claim 42 requires that the cells are cultured cells (page 10, lines 10-12).

Claim 43 requires that the vector is a retroviral vector (page 19, lines 36-37).

Claim 44 requires that the candidate agent is a peptide (page 16, line 25).

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 37-44 are rejected as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. This is a new matter rejection.

II. Claims 37-44 are rejected as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. This is a "possession" rejection.

III. Claims 37-44 are rejected as failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

IV. Claim 38 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

V. Claims 37, 40 and 42-43 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

VI. Claims 37, 40 and 42-43, as amended, are rejected under 35 U.S.C. § 103(a) as being obvious over Uhr (USP 5,612,185) for reasons of record.

VII. Claims 38 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Uhr in view of Hide.

VIII. Claim 43 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Uhr in view of Conneally for reasons of record as reiterated below.

IX. Claims 37 and 40-44 are rejected under 35 U.S.C. § 103(a) as being obvious over Nolan in view of Jia-ping and Uhr.

X. Claims 38 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr in view of Hide.

**ARGUMENT**

I. Claims 37-44 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection.

The written description requirement of 35 U.S.C. § 112, first paragraph, involves the question of whether the subject matter of a claim conforms to the disclosure of an application as filed. According to the MPEP, an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed?"[1] The subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement. Likewise, MPEP states that

1 See MPEP § 2163.02, citing *In re Gosteli* 872 F.2d 1008, 1012 (Fed. Cir. 1989).

newly added claim limitations may be supported by disclosure that is express, implicit, or inherent.[2]

In this Office Action, the Examiner argues that the new claims introduce new matter into the application. Each issue raised by the Examiner is set forth under a separate header below.

*Support for the claims does not need to be in one place in the specification*

On page 3 of the Office Action, the Examiner argues that support for a claim needs to be in one place in the specification. Specifically, the Examiner states that claim 37 of the instant application contains new matter because the claim "in its entirety (as a unit) is not supported in the as-filed application". On page 4 of the Office Action, the Examiner states that "Applicants cite disparate sections of the specification provided support for individual method steps or components recited in the general support of claim 37". In making the rejection, the Examiner provides an example of an application having claims that are supported in one contiguous section of the application ("Cf. with the claims of the parent issued patent US 6,897,031 ('031 patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35"); see Office Action, bottom of page 3. In the section bridging pages 9 and 10 of the Office Action, the Examiner argues that support for claims cannot be by "picking and choosing of disparate elements of the specification and arrange[sic] in a manner as presently claimed". In support for this statement, the Examiner cites Net MoneyIN, Inc. v. Verisign, Inc., 545 F.3d 1359 (Fed. Cir. 2008).

The Appellants submit that the Examiner has erred because the cited Net Money case is not a § 112, first paragraph, case. Rather, the Net Money case clarifies a test for anticipation under 35 U.S.C. §102(a). The Net Money case is not relevant to this rejection because § 112 and § 102 are different parts of the statute,

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2 MPEP § 2163: "The written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed. New or amended claims, which introduce elements or limitations, which are not supported by the as-filed disclosure, violate the written description requirement...While there is no *in haec verba* requirement, ***newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure***. (emphasis added)

and cases that are relevant to one are not relevant to the other. Furthermore, the Net Money case refers to analysis of a prior art document, not a patent specification.

Other than the Net Money case (which is not relevant to § 112, first paragraph), the Examiner has not cited any authority to support her assertion that support for a claim needs to be in one place in the specification (as a unit) and the Appellants cannot find any such requirement. In view of the above, the Appellants submit that this rejection lacks foundation and should be reversed.

To the extent that further discussion is necessary, element-by-element support for each of the appealed claims is provided in the table below. Particular issues raised by the Examiner are addressed after this table.

The following table indicates where support for the rejected claims can be found:

| Claim no. | Element | Support in instant application |
|---|---|---|
| **37** | general support for screening method | Page 3 line 36 to page 4 line 5 |
| **37** | "introducing" | Page 19, lines 32-34<br>Page 20, lines 1-2 |
| **37** | "$10^3$" | Page 10, line 9<br>Page 21 lines 1-2 |
| **37** | "vectors" | Page 19, lines 31-34 |
| **37** | "mammalian cells" | Page 10, line 20 |
| **37** | "in vitro" | Page 10 lines 10-12 |
| **37** | "physiological signal" | Page 9, lines 36-37<br>Page 34, line 5 |
| **37** | "at least *three* optical properties" | Page 4, line 3 |
| **37** | sequencing to identify agent | Page 28, lines 10-12<br>Page 43, line 20<br>Page 32, lines 34-36 |
| **38** | specific physiological signals | Page 34, lines 5-7 |
| **39** | "$Ca^{++}$ and ionomycin" | Page 34, line 6 |
| **40** | Specific optical properties | Page 34, line 37<br>Page 34, line 30 |

| | | |
|---|---|---|
| | | Page 10, lines 35-36 |
| **41** | "$10^6$" | Page 19, line 20 |
| **42** | "cultured cells" | Page 10, lines 10-12 |
| **43** | "retroviral vector" | Page 19, lines 36-37<br>Page 20, lines 1-2 |
| **44** | "peptide" | Page 16, line 25 |

*Mammalian* cells *grown in vitro*

In the section bridging pages 4 and 5 of the Office Action, the Examiner states "There is nothing in the above cited sections that recites mammalian cells grown *in vitro*" and also that "the $10^3$ refers to a library of cells and not to a library of $10^3$ vectors".

That the method can be done using mammalian cells is explicitly described on page 10, line 20, of the instant application:

> Preferred cell types for use in the invention will vary with the cellular phenotype to be modulated. Suitable cells include, but are not limited to, mammalian cells, including animal (rodents, including mice, rats, hamsters and gerbils), primates, and human cells, particularly including tumor cells of all

That the method can be done using cells grown *in vitro* is explicitly described at page 10, lines 10-14 of the instant specification:

> $10^8$ to $10^9$ being especially preferred. The population or sample can contain a mixture of different cell types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when , as outlined below. The cells may be in any cell phase, either synchronously or not, including M,

That the method can be done using a library of at least $10^3$ vectors is implicitly supported in the priority application at page 10, lines 8-10 (which states that the candidate agent may be contacted with at least $10^3$ cells) in combination with page 21 lines 1-2 (which states that the cells may contain a single vector).

Page 10, lines 8-10 of the instant application, which states that the candidate agent may be contacted with at least $10^3$ cells, is set forth below:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about $10^3$ being preferred, at least about $10^6$ being particularly preferred, and at least about $10^6$ to $10^9$ being especially preferred. The population or sample can contain a mixture of different cell

and page 10, lines 8-10, which states that the target cells may contain a single vector, is set forth below

> In addition, it is possible to configure a retroviral vector to allow inducible expression of retroviral inserts after integration of a single vector in target cells; importantly, the entire system is contained within the single retrovirus. Tet-inducible retroviruses have been designed incorporating the Self-

If there are at least $10^3$ cells each containing a single vector, then there is implicit support for $10^3$ vectors.

Appellants further note that the introduction of libraries of agents of various complexities into a population of cells is discussed on page 19 of the specification.

Based on the above, the phrase "at least $10^3$ vectors encoding different candidate agents into a population of mammalian cells grown *in vitro*" is fully supported in the instant application.

In view of the foregoing discussion, this part of the rejection may be reversed.

**Specific argument directed to claim 41**

To the extent that the argument set forth immediately above is not persuasive and this rejection is to be maintained because there is no *explicit* support for "$10^3$ vectors", the Appellants submit that explicit support for claim 41, which requires a library "of at least $10^6$ vectors" is found on line 20 of page 19. This section states that, in the context of a library, "at least $10^6$ ... different sequences are simultaneously analyzed in the subject methods".

Thus, if the Board believes that the rejection of claim 37 should be maintained because the specification does not describe $10^3$ vectors, the Board is requested to withdraw the new matter rejection of claim 41.

*Physiological signals*

In the section bridging pages 5 and 6 of the Office Action, the Examiner states that "subjecting" a population of cells to a physiological signal is not supported because the specification only recites "evaluating" cells in the presence or absence of a physiological signal.

The Appellants submit that evaluating cells in the presence or absence of a physiological signal implicitly requires that the cells are subjected to a physiological signal. As such, "subjecting" a population of cells to a physiological signal is implicitly supported in the specification.

In view of the foregoing discussion, this part of the rejection may be reversed.

*At least three optical properties*

In the section bridging pages 6 and 7 of the Office Action, the Examiner argues that support for "at least three optical properties" as claimed is not provided by the cited support (which recites "at least three, four or five cellular parameters").

However, the cellular parameters by which a cell is sorted are in fact optical properties. See, e.g., the entire application particularly the context given on page 34, lines 30-37, which states that parameters that are characteristic of a cell are measured by light scatter properties. Moreover, in the flow cytometry arts (and consistent with how the term is used in the instant application) a "parameter" corresponds to an optical property (e.g., fluorescence, side scattering, etc).

In view of the above, the Appellants submit that the cited support (which recites "at least three, four or five cellular parameters") provides more than adequate support for the phrase "at least three optical properties" as claimed.

In view of the foregoing discussion, this part of the rejection may be reversed.

*Sequencing to identify*

In the section bridging pages 7 and 8, the Examiner states that the cited passage on page 28, lines 10-12 does not provide support for the last element of the claims, i.e., sequencing the nucleic acid. Supplemental support for this element is found on page 32, lines 34-36, as shown below:

> In a preferred embodiment, the bioactive agent is characterized. This will proceed as will be appreciated by those in the art, and generally includes an analysis of the structure, identity, binding affinity and function of the agent. Generally, once identified, the bioactive agent is resynthesized and

Appellants submit that because the structure of a nucleic acid is defined by its nucleotide sequence, the "analysis of the structure" of a nucleic acid provides implicit support for sequencing the nucleic acid.

In view of the foregoing discuss, the Appellants submit that the Examiner has no reason to reject the claims as containing new matter. Reversal of this rejection is therefore requested.

II. Claims 37-44 are rejected as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. This is a "possession" rejection.

With respect to satisfying the written description requirement, even in an "unpredictable art," applicants "are *not* required to disclose *every* species encompassed by their claims . . . ."[3] Otherwise, to claim a genus, every species within a genus would have to be explicitly described. This is **not** the law. In other words, the written description requirement does not require a specific description of every species encompassed by a claim.

Furthermore, the Written Description Guidelines (Federal Register Vol. 66 No. 4, dated January 5, 2001), using no uncertain terms, state that the specification of a patent application need only described in detail that which is new or not conventional. For example, on page 1105 of the Guidelines it is stated: "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of skill in the art" Also, on page 1105 of the Guidelines it is stated: "Information which is well known in the art need not be described in detail in the specification". On page 1106, the Guidelines state: "The description need only describe in detail that which is new or not conventional"

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3 *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218, (C.C.P.A. 1976).

and "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail".

This rejection is largely based on whether a library of $10^3$ vectors encoding different candidate agents are adequately described. See, e.g., "The specification at the time of filing does on describe a library $10^3$ vectors" (p. 15), "It does not describe all or any kinds of vectors" (p. 15), "there is no description of a candidate agent that has been isolated or identified" (p. 16), "the specification reference is made ... not to a $10^3$ library that encodes an enormous numbers of different kinds of candidate agents" (p. 16), "Nor is there a description of the candidate agents that alters any or all kinds of phenotypes" (p. 16), "There are no characterizing features of the genus candidate agent coupled with a functional limitation or core sequences" (p. 16). Appellants traverse.

To the extent that this rejection is not already addressed in the Appellants' traversal of the new matter rejection above, the Appellants submit that the instant specification is replete with description about how the claimed method may be performed. See, e.g., pages 8-41. With specific reference to the libraries of vectors (which appears to be a focal point for the Examiner), the Appellants submit that such libraries are generically described in the instant specification at, e.g., page 19, line 31 to page 21, line 11. Moreover, libraries of vectors are conventional in the art (see, e.g., WO97/27212), which is cited by the Examiner in an obviousness rejection that is discussed below. Thousands of other publications describe the production and use of libraries of vectors. Since the guidelines clearly state that "the description need only describe in detail that which is new or not conventional" and "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail", there is no need for the Appellants to provide a detailed description of libraries of vectors that can be used in the rejected claims. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work.

Finally, to the extent that this rejection is based on the lack of a reduction to practice (see further comments on page 16 of the Office Action, e.g., "no identification of a candidate peptide agent has been made"), the Appellants submit that even in the biotechnology arts a reduction to practice is not required for written description. See MPEP § 2163: "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Citing *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084. The amount of guidance in the instant application alone should be adequate description of this aspect of the appealed claims.

In view of the foregoing discussion, the Appellants submit that there is an adequate written description of what is being claimed. Reversal of this rejection is requested.

**Specific argument directed to claim 41**

Again, to the extent that the argument set forth immediately above is not persuasive and this rejection is to be maintained because there is inadequate written description for "$10^3$ vectors", the Appellants submit that explicit support for claim 41, which requires a library "of at least $10^6$ vectors" is found on line 20 of page 19. This section states that, in the context of a library, "at least $10^6$ different sequences are simultaneously analyzed in the subject methods".

Thus, if the Board believes that the rejection of claim 37 should be maintained because the specification does not describe $10^3$ vectors, the Board is requested to withdraw the rejection of claim 41.

III. Claims 37-44 are rejected as failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The law relating to enablement is well established.
When rejecting a claim under the enablement
requirement of section 112, the PTO bears an

> initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application.

*In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993)

> "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive'".

*PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of hot to practice a desired embodiment of the invention claimed.

*PPG Indus.*, 75 F.3d 1564 (quoting *Ex parte Jackson* 217 USPQ 804 807 (BPAI 1982))

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1998).

Like the written description rejection addressed above, this rejection is based on whether one of skill in the art can make and use a library of vectors encoding candidate agents in the claimed method. In making the rejection, the Examiner states that "The specification provides only broad generalized statements. It would take an undue amount of experimentation to determine the $10^3$ library of vectors encoding different candidate agents that alters any type of phenotype to any kind of cells in a population". Office Action, page 20. Specifically, the Examiner alleges that "The specification fails to give adequate direction and guidance in how to make the $10^3$ library of vectors" (Office Action, page 20, last line) and "Applicants have failed

to provide any working examples for a $10^3$ library of any kind of vectors" (Office Action, page 21), and "The state of the prior art is such that the consequences of some bioactive agents and cell interaction on some cells have not yet been fully determined or elucidated" (Office Action, page 21, last line) and, while acknowledging that the level of skill in the art is high (page 22), the Examiner states that "the molecular library and gene art is so unpredictable that it would require "undue experimentation to make the invention" (page 22). Examiner states that a "candidate bioactive agent" is an example of what is unpredictable. See page 22, last line.

The Board is requested to apply the arguments in the prior section of this response to this rejection. Specifically, the Appellants submit that libraries of vectors are conventional in the art and, as such, their making and use does not require undue experimentation. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work. Furthermore, pre-knowledge of the structure and function of the candidate agents would undermine the purpose of the invention.

Moreover, to the extent that this rejection is based on the lack of a reduction to practice (see further comments on page 23 and 24 of the Office Action, e.g., "The single working example teaches...." and "There is not a single working example", the Appellants submit that even in the biotechnology arts a working example is not required for enablement. See MPEP § 2164.02: "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." The vast amount of guidance in the instant application, combined with what is already routine in the art, should enable the appealed claims.

The Appellants submit that this rejection has been adequately addressed. Reversal of this rejection is requested.

IV. Claim 38 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The MPEP states that one of the requirements set forth in 35 U.S.C. § 112, second paragraph is that the claims must particularly point and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. This requirement is an objective one and is evaluated in the context of "whether the claim is definite - i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." (see MPEP § 2171). Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph. (see MPEP § 2173.04).

To comply with § 112, ¶ 2, a claim must "particularly point out and distinctly claim the subject matter which the applicant regards as his invention." The courts have stated that "[c]laims are considered indefinite when they are 'not amenable to construction or are insolubly ambiguous . . . . Thus, the definiteness of claim terms depends on whether those terms can be given any reasonable meaning.'" *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1346 (Fed. Cir. 2007) (quoting *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005)). In other words, an indefiniteness inquiry "requires a determination whether those skilled in the art would understand what is claimed." *Id.*

On page 25 of the Office Action, the Examiner rejects claim 38 as being indefinite because it recites the term "cells". The Examiner believes that the claim is indefinite because it is unclear whether the cells used to stimulate a physiological signal in claim 38 "are the same or different from the mammalian cells that serve as physiological signal". While this rejection is itself unclear because it is not clear what the Examiner means by "mammalian cells that serve as physiological signal" (which phrase is not in claims 37 or 38), it is implicit that the physiological signals called out in claim 38 are different from the population of cells subjected to the physiological

signal, as called out in claim 37. Any other interpretation does not make sense, since the cells in the population of cells are already subjected to each other.

Reversal of this rejection is requested.

V. Claims 37, 40 and 42-43 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

On page 25 of the Office Action, the Examiner argues that "the as-filed specification does not provide support for the new claim limitation of the broad claim "cells" in claim 38 or the two steps as recited in claim 37".

Appellants do not understand this rejection, particularly because the entire application is directed to a cell screening assay. Specifically, the terms "cell", "cells" and "cellular" are found at hundreds of positions in the instant application. Indeed, "a population of cells" is defined on page 10, and support for cells used as a physiological signal is found on page 34, line 5.

Reversal of this rejection is requested.

VI. Claims 37, 40 and 42-43 are rejected under 35 U.S.C. § 103(a) as being obvious over Uhr (USP 5,612,185) for reasons of record.

According to the Examiner, "Uhr, alone, discloses or teaches all the elements of the claim except the sequencing of the candidate agents." Appellants respectfully disagree.

Uhr discloses a process for treating cancer by placing tumor cells in cell cycle arrest (col. 2, lines 62-65). Uhr discloses that cell cycle arrest may be induced by gene therapy, e.g., by introducing nucleic acid encoding c-fos or c-jun directly into tumor cells (col. 22, lines 6-10) or using anti-idiotypic antibodies (see abstract). Uhr also contemplates the use of retroviral vectors to deliver genes that place tumor cells in cell cycle arrest (col. 22, lines 14-19). Uhr proposes to produce mice that contain transplanted cells that have modified *in vitro* (col. 22, lines 48-50). Uhr also discloses

using FACS to analyze the spleens of mice into which cells have been transplanted (col. 2, lines 64-65). Uhr's Example 4 (starting in col. 31) describes methods by which tumor cells, grown *in vitro*, can be treated with an agent (e.g., an anti-Ig) to induce cell cycle arrest and then killed. In one embodiment described in col. 32 lines 21-37, tumor cells are treated with ligands for cell surface receptors to determine the optimal conditions for cell cycle arrest. In the embodiment described in col. 32, lines 38-49, the arrested cells are contacted with toxins and agents, and transferred into native recipients for further analysis.

Uhr's disclosure is deficient for a number of reasons.

*Uhr does not teach the use of a library of at least $10^3$ vectors encoding different candidate agents*

Uhr does not teach the use of a library of *at least $10^3$ vectors encoding different candidate agents*, as required by the rejected claims. Uhr describes the use of a vector that encodes c-jun or c-fos into cells to induce cell cycle arrest. These proteins were chosen by Uhr because they are thought to induce cell cycle arrest. Thus, at best, Uhr suggests a method that employs one of two vectors (which encode c-jun or c-fos). Based on Uhr's disclosure, there would be no reason to use more than two different vectors, let alone at least 1,000 vectors as required by the rejected claims.

On page 27 of the Office Action, the Examiner argues that Uhr's Fig. 3 indicates a library of at least $10^3$ vectors. However, as explained in col. 17 lines 46-67, Fig. 3 is simply an RT-PCR assay of $BCL_1$ and CCALC (cell cycle arrested cells) cells. mRNA was made from cells, and the mRNA was assayed for the expression of myc, fos and β-actin. Uhr's Fig. 3 provides no evidence that Uhr discloses "a library of at least $10^3$ vectors encoding different candidate agents" much less introducing such a library into a population of mammalian cells grown *in vitro*.

In the Office Action, the Examiner also argues that because Uhr refer to gene in the plural, i.e., states that "DNA encoding key gene**s** such as, for example, c-fos or c-jun, may be applied directly to cells....." (Uhr, col. 22; emphasis added by the

Examiner), then Uhr teaches the use of a library of at least $10^3$ vectors. However, put into context (see below) that sentence merely states that cell cycle arrest can be induced by gene therapy using, e.g., fos ***or*** jun.

> Ultimately, it is contemplated that tumor cell cycle arrest may be induced by gene therapy. DNA encoding key genes in this process, such as, for example, c-fos or c-jun, may be applied directly to cells, in the form of oligonucleotides, or other genetic constructs. It has been shown that oligonucle-

Because: a) gene therapy usually uses single genes (not "a library of at least $10^3$ vectors encoding different candidate agents", as required by the claims) and b) Uhr refers to fos and jun in the alternative (i.e., using the word "or") it is clear that Uhr neither teaches or suggests the use of a library of at least $10^3$ vectors encoding different candidate agents", as required by the claims.

On page 29 of the Office Action, the Examiner explains that because the flow cytometry results shown in Fig. 1 of Uhr was done using $10^3$ cells ("Since there may be at least $10^3$ cells, it necessarily follows that there were at least $10^3$ vectors"). However, this makes no sense because, as explained in the paragraph bridging cols. 16 and 17, the results shown in Fig. 1 show FACS plots of various spleens. There are no vectors in the cells of Fig. 1, let alone over 1,000 vectors.

Reversal of this rejection is requested for this reason.

*Uhr does not introduce candidate agents into cells and subject the cells to a physiological signal as separate events*

Uhr does not introduce candidate agents into cells *and* subject the cells to a physiological signal as separate events, as required by the rejected claims. Uhr merely introduces a gene (c-jun or c-fos) into cells to induce cell cycle arrest. At best, the compounds can either be considered candidate agents (in which case there is no separate physiological stimulus) or as physiological stimuli (in which case there is no candidate agent). Either way, introducing candidate agents into cells *and* subjecting the cells to a physiological signal as separate steps is not disclosed by

Uhr. Moreover, since the general goal of Uhr's method is to identify compounds that induce cell cycle arrest, at best Uhr teaches an assay that involves no more than determining whether a compound causes a cell to arrest. That is not the method being claimed.

In the Office Action, the Examiner argues that introducing of the candidate agents into cells *and* subjecting the cells to a physiological signal did not have to be separate events. Appellants believe that the claims are clear on this matter

On page 30 of the Office Action, the Examiner attempts to rebut this argument by stating that "the step of "subjecting" is not supported in the as-filed specification". The Examiner is incorrect. Claim 34, lines 5-7 clearly states that "The cells may be evaluated in the presence or absence of physiological signals", which implicitly means that there is a subjecting step.

This rejection may be reversed for another reason.

*Uhr does not disclose using FACS to examine the individual cells in the cell population that has been grown in vitro*

Uhr does not disclose using FACS to examine the individual cells in the cell population that has been grown *in vitro*. The only FACS methods described in Uhr's disclosure are those in which the cells of spleens of animals are examined. Such cells are grown *in vivo* rather than *in vitro* and, as such, this element of the claims is not provided by Uhr.

In the Office Action, the Examiner argues that cells grown *in vitro* are described in Example 4 of the specification, e.g., in col 31 (see below).

> To allow the more rapid development of further work, the inventors have established a $BCL_1$ line, 3B3, that replicates every three days in vitro and which is tumorigenic. This particular cell line grows slightly faster than in vivo passaged $BCL_1$ but is fully susceptible to induction of dormancy when $BCL_1$ is injected into either Id-immune or SCID mice receiving rabbit anti-Id antibody. The 3B3 in vitro cell line will be especially useful for investigating the kinetics of gene induction following anti-Ig treatment, and will facilitate the introduction of DNA constructs, by transfection and subsequent selection, to investigate the role of oncogene expression in dormancy induction.

However, *in vitro* cells described in this passage are not analyzed by FACS. Rather, they are injected into mice. See, e.g., the paragraph at col. 31, lines 49-64, provided above. There is no indication that the cells described in the above paragraph are examined by FACS, as discussed above.

On page 32 of the Office Action, the Examiner argues that Uhr's Example 4 "teaches the advantage of in vitro over in vivo and teaches in Fig. 1 the FACS sorting of cells in vitro." However: a) Example 4 makes no mention of performing FACS on cells grown in vitro and b) the plots shown in Fig. 1 are of splenocytes grown *in vivo* (not in vitro). See, e.g., the paragraph bridging cols. 26 and 27.

Since there is no disclosure in Uhr of using FACS to examine the individual cells in the cell population that has been grown *in vitro*, Uhr fails to teach another element of the claims.

Reversal of this rejection is requested.

*Uhr does not disclose sequencing the nucleic acid encoding the candidate agent in a cell that has an altered phenotype*

Uhr does not disclose sequencing the nucleic acid encoding the candidate agent in a cell that has an altered phenotype. Since the identities of Uhr's clones (which, at best would encode c-jun or c-fos) would be known before any experiments were initiated, there would be no need for this step to be performed.

On page 33 of the Office Action, the Examiner makes reference to a sentence in Uhr that states that antibody idiotypes can be identified by sequence analysis. However, in Uhr's method, antibody encoding sequences are not introduced into a population of mammalian cells. Rather, the antibodies are contacted with cells, and the interaction between an antibody and a marker on the surface of a cell causes cell cycle arrest.

Finally, the Examiner argues that Uhr teaches sequencing because "the disclosure does not define any sequencing step or any candidate agent that has been identified such that sequencing is done". However, this makes no sense because the instant application has no bearing on what Uhr does or does not teach.

Thus, Uhr is deficient for many reasons. Reversal of this rejection is requested.

VII. Claims 38 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Uhr in view of Hide.

The teachings and deficiencies of Uhr are discussed above.

Hide is cited solely to provide a FACS-based method for assaying a population of cells that have been stimulated by $Ca^{++}$ or ionomycin.

However, none of Uhr's deficiencies discussed above is met by Hide's disclosure and, as such, taken in any combination, Uhr and Hide fail to teach or suggest all of the elements of the rejected claims.

Moreover, it is completely unclear how Hide's method could be integrated into Uhr's method because Uhr's method is highly focused on inducing cell cycle arrest, and killing cells that are in cell cycle arrest. How and why stimulating cells $Ca^{++}$ or ionomycin would be used in Uhr's method is not clear from the record.

Reversal of this rejection is therefore requested.

VIII. Claim 43 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Uhr in view of Conneally for reasons of record as reiterated below.

The teachings and deficiencies of Uhr are discussed above.

Conneally is cited solely to provide the subject matter of claim 43, i.e., a suggestion to use retroviral vectors. However, none of Uhr's deficiencies discussed above is met by Conneally's suggestion to use retroviral vectors and, as such, taken in any combination, Uhr and Conneally fails to teach or suggest all of the elements of the rejected claims.

Reversal of this rejection is therefore requested.

IX. Claims 37 and 40-44 are rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Nolan (WO 97/27212) in view of Jia-Ping and Uhr.

The Appellants submit that Nolan cannot preclude the patentability of the rejected claims for the reasons set forth below.

This instant application's earliest priority date is April 17, 1998, as indicated on the filing receipt and the application data sheet of this application. The relevant section of the filing receipt is reproduced below for the Board's convenience.

**Domestic Priority data as claimed by applicant**

This application is a CIP of 09/157,748 09/21/1998 PAT 6,461,813 which is a CIP of 09/062,330 04/17/1998 PAT 6,897,031

Thus, the instant application claims priority to an application (09/062,330) that was filed on April 17, 1998. The following table indicates support for the rejected claims in the instant application, and in the parent application.

| Claim no. | Element | Support in instant application | Support in parent application |
|---|---|---|---|
| 37 | general support | Page 3 line 36 to page 4 line 5 | Page 3 lines 11-30 |
| 37 | "introducing" | Page 19, lines 32-34 | Page 24, line 29 to page 25, line 2 |

| | | | |
|---|---|---|---|
| | | Page 20, lines 1-2 | |
| **37** | "$10^3$" | Page 10, line 9<br>Page 21 lines 1-2 | Page 24, lines 25-26<br>Page 26 line 18 |
| **37** | "vectors" | Page 19, lines 31-34 | Page 25, line 1 |
| **37** | "mammalian cells" | Page 10, line 20 | Page 18, line 22 |
| **37** | "in vitro" | Page 10 lines 10-12 | Page 8, line 27 |
| **37** | "physiological signal" | Page 9, lines 36-37<br>Page 34, line 5 | Page 8, lines 17-18 |
| **37** | "at least *three* optical properties" | Page 4, line 3 | Page 3, line 12 |
| **37** | sequencing to identify agent | Page 28, lines 10-12<br>Page 43, line 20<br>Page 32, lines 34-36 | Page 36, lines 5-7<br>Page 40, lines 15-20 |
| **38** | specific physiological signals | Page 34, lines 5-7 | Page 8, lines 17-19 |
| **39** | "$Ca^{++}$ and ionomycin" | Page 34, line 6 | Page 8, line 18 |
| **40** | Specific optical properties | Page 34, line 37<br>Page 34, line 30<br>Page 10, lines 35-36 | Page 9, line 25<br>Page 7, lines 30-33<br>Page 7, line 5 |
| **41** | "$10^6$" | Page 19, line 20 | Page 24, line 20 |
| **42** | "cultured cells" | Page 10, lines 10-12 | Page 8, lines 25-26 |
| **43** | "retroviral vector" | Page 19, lines 36-37<br>Page 20, lines 1-2 | Page 18, line 22 |
| **44** | "peptide" | Page 16, line 25 | Page 21, line 13 |

Nolan's publication date (July 31, 1997) predates the earliest priority date of this application (April 17, 1997) by less than a year. As such, Nolan only qualifies as prior art only under 35 U.S.C. § 102(a)[4].

A Declaration under 35 U.S.C. § 1.131 (the "Fisher Declaration"; submitted herein in the Evidence Appendix of this brief) was submitted with the Appellants'

[4] The PCT application upon which Nolan's publication (WO97/27212) is based was filed on January 23, 1997. Nolan's filing date is *prior to* the November 19, 2000 date of enactment of amended 35 U.S.C. § 102(e). As such, Nolan is not available as prior art as of its filing date, and is not citable as "102(e)-type art".

response dated July 24, 2006, in order to obviate a rejection over a similar combination of references (i.e., Nolan in view of Jai-ping or Ryan). The Fisher Declaration establishes invention of the subject matter of the rejected claims prior to the Nolan's publication date and, as such, Nolan cannot preclude the patentability of the instant claims.

In maintaining this rejection, the Examiner argues that the ~~Applicant~~Appelant's priority application does not provide support for the newly presented claims, and, as such, the Nolan publication is 102(b)-type art and cannot be antedated. Specifically, the Examiner argues that, for example, "a library of at least $10^3$ vectors", "subjecting the population of cells to a physiological signal", "at least 3 optical properties" and "sequencing" are not described in the priority application.

Support for each element of the claims in the priority application is provided in the table above. Exemplary support for each of the four elements that the Examiner has an issue with is discussed below

*"A library of at least $10^3$ vectors"*

That the method can be done using a library of at least $10^3$ vectors is implicitly supported in the priority application at page 24, lines 24-27 (which states that the candidate agent may be contacted with at least $10^3$ cells) in combination with page 22 lines 17 and 18 (which states that the cells may contain a single vector). If there are at least $10^3$ cells each containing a single vector, then there is implicit support for $10^3$ vectors.

Page 24, lines 24-27 of the priority application, which states that the candidate agent may be contacted with at least $10^3$ cells, is set forth below:

> The candidate bioactive agents are combined or added to a cell or population of cells. Suitable cell types for different embodiments are outlined above. By "population of cells" herein is meant at least two cells, with at least about $10^3$ being preferred, at least about $10^5$ being particularly preferred, and at least about $10^8$ being especially preferred.

and page 22 lines 17 and 18, which states that the target cells may contain a single vector, is set forth below

In addition, it is possible to configure a retroviral vector to allow inducible expression of retroviral inserts after integration of a single vector in target cells; importantly, the entire

Based on the above, the Appellants submit that the phrase "at least $10^3$ vectors encoding different candidate agents" is fully supported in the priority application.

**Specific argument directed to claim 41**

To the extent that the argument set forth immediately above is not persuasive and this rejection is to be maintained because there is no *explicit* support for "$10^3$ vectors", the Appellants submit that explicit support for claim 41, which requires a library "of at least $10^6$ vectors" is found in the priority application on line 20 of page 24. This section states that, in the context of a library, "at least $10^6$ ..... different sequences are simultaneously analyzed in the subject methods".

Thus, if the Board believes that the rejection of claim 37 should be maintained because the specification does not describe $10^3$ vectors, the Board is requested to withdraw the new matter rejection of claim 41.

*"Subjecting the population of cells to a physiological signal"*

That the method can be done by subjecting a population of cells to a physiological signal is implicitly supported in the priority application at page 24, lines 24-27 (pasted below).

one another. For example, the cells may be evaluated in the presence or absence of physiological signals, such as exocytic inducers (i.e, $Ca^{++}$, ionomycin, etc.), hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, or other cells (i.e. cell-cell contacts). In another example, the measurements of exocytosis are

Evaluating cells in the presence or absence of a physiological signal implicitly requires that the cells are subjected to a physiological signal. As such, "subjecting" a population of cells to a physiological signal is implicitly supported in the specification.

In view of the foregoing discussion, this part of the rejection may be reversed.

*"At least 3 optical properties"*

Explicit support for at least 3 optical properties is found in the priority application at page 3, lines 12-13:

> different conditions or combined with different bioactive agents. The methods comprise sorting the cells in a FACS machine by assaying for alterations in at least three of the properties selected from the group consisting of light scattering, fluorescent dye uptake,

Similar wording also found at, e.g., page 9 line 6, for example.

*"Sequencing"*

Support for "sequencing" is found in the priority application at page 40 lines 15-17, shown below:

> In a preferred embodiment, the bioactive agent is characterized. This will proceed as will be appreciated by those in the art, and generally includes an analysis of the structure, identity, binding affinity and function of the agent. Generally, once identified, the

Appellants submit that because the structure of a nucleic acid is defined by its nucleotide sequence, the "analysis of the structure" of a nucleic acid provides implicit support for sequencing the nucleic acid.

In view of the foregoing discussion, the Appellants submit that the priority application fully supports the instant claims. As such, the Nolan is disqualified as a prior art reference and cannot preclude the patentability of the instant claims. Thus, this rejection should be reversed.

X. Claims 38 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr in view of Hide.

This rejections is also predicated on the claims not being supported by earlier filed application serial no. 09/062,330, now issued as U.S. patent 6,897,031.

The claims are submitted to be fully supported in the instant application and in parent application serial no. 09/062,330, now issued as U.S. patent 6,897,031 (see table above). As such, the Fisher declaration antedates Nolan's publication date, and Nolan cannot preclude the patentability of the rejected claims.

Reversal of this rejection is respectfully requested.

In view of the foregoing discussion, the Appellants request that all rejections be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,
Bozicevic, Field & Francis, LLP

Date: November 22, 2011

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
(650) 327-3400 main
(650) 327-3231 fax

## CLAIMS APPENDIX

37. A method, comprising:

introducing a library of at least $10^3$ vectors encoding different candidate agents into a population of mammalian cells grown *in vitro*;

subjecting the population of cells to a physiological signal, wherein said physiological signal stimulates a phenotype in said cells in the absence of the candidate bioactive agents;

sorting the individual cells in the population on the basis of at least three optical properties by fluorescent activated cell sorting (FACS),

identifying a cell having a phenotype that is altered relative to other cells in the population; and

sequencing the nucleic acid encoding said candidate agent in said cell that has an altered phenotype, thereby identifying said candidate agent in said cell.

38. The method of claim 37, wherein said physiological signal is an exocytic inducer, a hormone, an antibody, a peptide, an antigen, a cytokine, a growth factor, an action potential or cells.

39. The method of claim 38, wherein said exocytic inducer is $Ca^{++}$ or ionomycin.

40. The method of claim 37, wherein said at least three optical properties comprise at least one optical property selected from the group consisting of: light scattering, and fluorescent dye uptake, fluorescent dye release and binding of a fluorescent antibody.

41. The method of claim 37, wherein said library is of at least $10^6$ vectors in size.

42. The method of claim 37, wherein said cells are cultured cells.

43. The method of claim 37, wherein said vector is a retroviral vector.

44. The method of claim 37, wherein said candidate agent is a peptide.

## EVIDENCE APPENDIX

Submitted herewith is a declaration under 1.131 by Fisher.

| DECLARATION OF JOSEPH FISHER UNDER 37 C.F.R. §1.131 | Application Number | 09/293,670 |
|---|---|---|
| | Confirmation Number | 5176 |
| | Filing Date | April 16, 1999 |
| | First Named Inventor | Joseph Fisher |
| | Examiner | Teresa Wessendorf |
| | Group Art | 1639 |
| | Attorney Docket No. | RIGL-036CIP |

This Declaration with the attached Exhibits are being submitted in conjunction with the Applicants' Response to the Office Action dated February 24, 2006.

I, Joseph Fisher, M.D. Ph.D. do hereby declare as follows.

1. I am listed as an inventor of the above-referenced patent application.

2. Between June and September, 1997, I was a Scientist at Rigel Pharmaceuticals, Inc. (hereinafter "Rigel"). During this time, I was part of a program focused on the discovery of intracellularly-active peptides. The strategy employed by this program involved infecting cells with a library of retroviral vectors encoding candidate peptides, and selecting cells with an altered phenotype using fluorescence activated cell sorting (FACS)-based methods. The idea of using more than five FACS parameters to identify retrovirally-delivered, intracellularly-active peptides was developed before July 31, 1997.

3. I understand that the claimed subject matter of the above-referenced patent application relates to screening methods that include sorting a population of retrovirally infected cells using at least five fluorescence activated cell sorting (FACS) parameters. I

have been asked to provide factual evidence relating to my activities at Rigel with respect to the claimed subject matter before and after July 31, 1997.

4. Experiments confirming the applicability of FACS-based screening methods that employ at least five FACS parameters to the discovery of retrovirally-delivered intracellularly-active bioactive peptides were performed prior to July 31, 1997.

5. Exhibit A, which is a copy of pages 24 and 25 of my laboratory notebook, describes the results of an experiment in which cells were treated to induce exocytosis, and sorted using five FACS parameters. Exhibit A is dated prior to July 31, 1997. The top four graphs of page 25 show FACS results obtained from DMSO-treated cells (control), and the bottom four graphs of page 25 show FACS results obtained from A23187-treated cells (experimental). The top left graph of each group of four graphs shows results obtained from the parameter used to detect FM143, a fluorescent dye. The top right graph of each group of four graphs shows results obtained from the parameter used to detect FITC, another fluorescent dye. The bottom left graph shows results obtained from the parameter used to detect propidium iodide. The bottom right graph shows results obtained from parameter used to detect front light scatter as well as, independently, the parameter used to detect side light scatter. Thus, Exhibit A demonstrates the applicability of FACS methods that employ at least five FACS parameters to the discovery of retrovirally-delivered intracellularly-active bioactive peptides, before July 31, 1997.

6. Exhibit B, which is a copy of pages 112 to 120 of my laboratory notebook, describes an experiment in which and MC9 and CEM cells are transfected with a library of retroviral vectors that encode peptides. Exhibit B demonstrates that CEM and MC9 cells were transfected with a library of retroviral vectors between August 22 and August 27, 1997.

7. In September 1997, a method that included infecting cells with a library of retroviral vectors encoding candidate bioactive peptides, and selecting cells with an altered phenotype using five fluorescence FACS parameters was reduced to practice.

8. Exhibit C, which is a copy of pages 138 and 139 my laboratory notebook, describes an experiment in which retroviral vector library-infected cells are stimulated staurosporine to induce apoptosis, and sorted using five FACS parameters: side scatter ("ssc"), front light scatter ("fsc"), and three separate fluorescence parameters: ("fl1", "fl2" and "fl3"). Results for control cells not contacted with staurosporine are shown in the graphs on the left hand side of page 139, and results for experimental staurosporine-treated cells are shown in the graphs of the right hand side of page 139. Thus, Exhibit C demonstrates reduction to practice of a method that includes infecting cells with a library of retroviral vectors encoding candidate bioactive peptides, and selecting cells with an altered phenotype using five FACS parameters, on September 8, 1997.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: June 25, 2006

Joseph Fisher, M.D. Ph.D.,

Attachments: Exhibits A - C

Project No.____

Book No._____ TITLE _____

Page No.____

# EXHIBIT A

HMC-1 - Exocytosis Trace Dyes

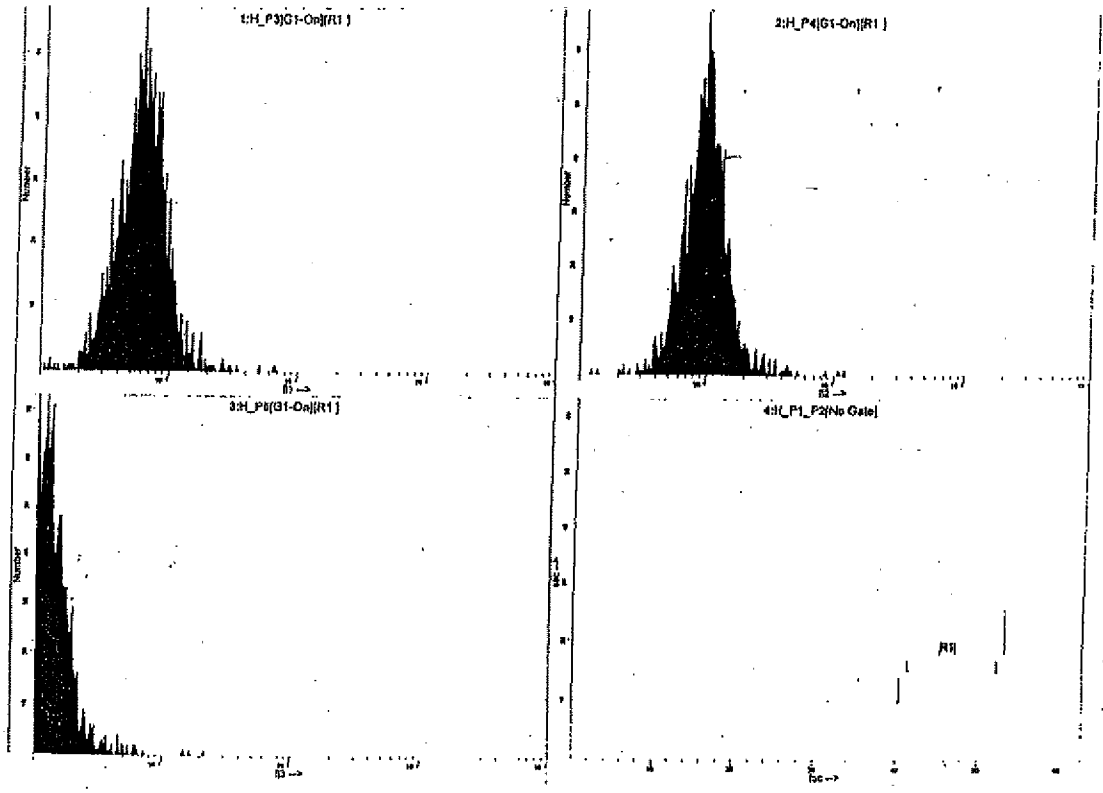
- Try FM-143 and ConA FITC as exocytosis Tracers on HMC-1 Cells.
- HMC-1 Cells - From Alexis Spinner ~ $10^6$ Cells/ml, Highly Viable
- Spin/Wash $5 \times 10^6$ Cells in MT
- Divide into 2 - ½ Incubate in MT 10' 37°C
  " " " + Succinyl ConA 100ug/ml } 37°C 10'
- Wash SOA Cells 2x MT
- Take up Cells in 1ml MT (no BSA) in 4 Tubes
  A) DMSO } + FM-143 - 2.5 ug/ml => 37°C 10'
  B) + A23187 1ug/ml }
  C) DMSO } + Con-A-FITC 25 ug/ml => "
  D) A23187 " }

Wash Cells 1x in MT - Take up in 1ml MT for FACS

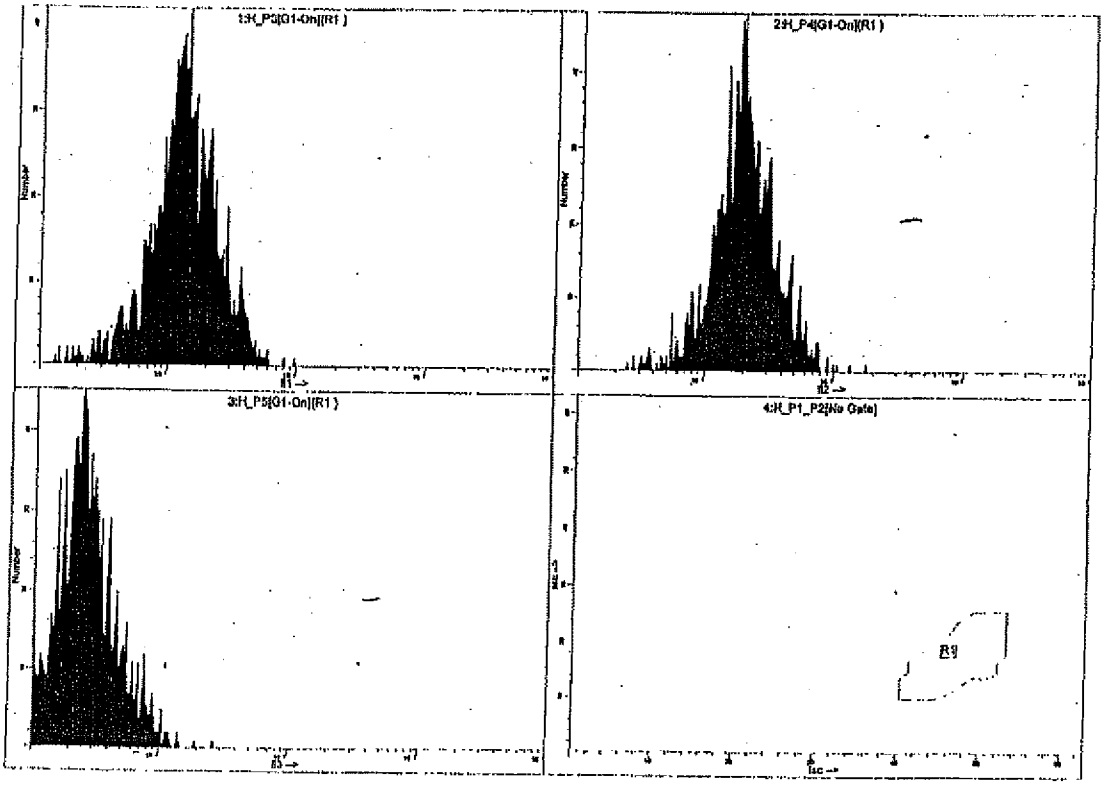
Saved Files as JMF012.001 } C
2 } D
3 } A
4 } B

To Page No.____

| Witnessed & Understood by me, | Date | Invented by | Date |
|---|---|---|---|
| | | | |




DMSO 10'
37°C




1ug/ml
AR3187 10'
37°C

To Page No.

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| essed & Understood by me, | Date | Invented by | Date |
| | | Recorded by | |

8/22/97

# EXHIBIT B

**Phoenix E Cell Transfection** ⇒ for MC9 cell Infection

- Use Susans Protocol (x2) So 2 wells of 6 well Plate / Transfection
- DNA - From Jenny Wang

| | | | | | |
|---|---|---|---|---|---|
| 1 | (10µg) = 6.6λ | | | | Rab3a and Synaptotagmin |
| 2 | 6.3λ | | | | Constructs |
| 3 | 8.9λ | | | | |
| 4 | 9.1λ | | Randy's Nomenclature | Jim's Nomenclature | |
| 5 = New IRes Hook | | 43-13 | 129.13 | 10µg = 11.6λ | |
| 6 = " " GFP | | 010.25 | 010-25 | 10µg = 11.1λ | |

From Jim L

- Follow Susans Protocol - Put Precipitate / Chloroquine on cells at 11AM
- Nice Peppery Precipitate Seen on all Transfectants

Protocol on next Page.

7PM ⇒ Aspirate DNA
- Wash 1x w/ Phoenix Media
- Add 2ml/well Fresh Media

# Protocol for transfection of Phoenix cells and infection of nonadherent target cells

## Day 1:
seed Phoenix cells (Es or As) in 6 well plates at $8x10^5$cells in 1.5 ml (DMEM + 10% FBS + P/S) per well

## Day 2: $CaPO_4$ Transfection

**per well:**
- 5ug DNA
- 30.5ul 2M $CaCl_2$
- 219ul $H_2O$
- 250ul 2X HBS

2 wells
- 10ug DNA
- 61λ 2M CaCl2
- 438λ $H_2O$
- 500λ 2X HBS

allow all reagents to come to room temperature 30mins. before starting (do not warm up in $H_2O$ bath)

add 50mM chloroquine at 2ul/well (50um final)

**mix $CaPO_4$ reagents in 15ml polypropylene tube:**
pipet 5ug DNA to side of tube
pipet 30.5ul of 2M $CaCL_2$ away from the DNA
mix the two together with the addition of 219ul of miliQ $H_2O$
then using a 1ml pipet, add 250ul of 2X HBS and quickly bubble air through the pipet for 2 to 10 secs. (the time is 2 HBS batch dependent)
immediately add mixture dropwise to well
microscopically visible precipitate should appear within a few minutes

**incubate 8hrs**
remove medium, wash once, and replace with 1.5ml medium

## Day3:
move transfected plates to $32^0C$

## Day 4: Infection of target cells
collect virus supernatent from transfected wells (1.5 ml) into 15 ml tubes and add either 1.5ul of 5mg/ml polybrene or 1.5ul 5mg/ml protamine sulfate
cfg out cells and debris at 2500 RPM for 5 mins. or alternatively, filter through .45um acrodisc syringe filter
count target cells and distribute $5x10^5$ cells per virus supe to 15ml tubes and pellet 5 mins. 2500 RPM
resuspend each pellet of target cells with virus supe and transfer to one well of a 24 well plate
seal plate with parafilm and cfg at RT for 90 mins. at 2500 RPM
Remove parafilm and incubate plate over night at $32^0C$

## Day 5:
collect and pellet each well of target cells and resuspend in 4ml and transfer each to a 6cm plate

## Day 7 or Day 8:
at 48 to 72 hrs. post infection target cells are ready to analyze for expression



| essed & Understood by me, | Date | Invented by | Date |
|---|---|---|---|
| | | Recorded by | 8/22/97 |

8/23/97

- Transfections of ϕE Cells (Cont.)
- This morning. 24 hrs post Transfection Start
  Look at Cells by Fluorescence.
  GFP ⊕ Cells Seen in #3, 4, and 6
  3 and 4 must be CTIG Vector (inducable with Ires GFP)
  1 and 2 " be pop Hook vector.
- Remove old Media
- Add 2ml/well of Warmed MC9 Media - 12PM

MC9 Positive Control Peptides

MC9 Cells - WT

| | | |
|---|---|---|
| Scaffold Hook | ~75% Hook+ | From Amy |
| Synaptotagmin | ~50% " | |
| RAB | ~ " " | |

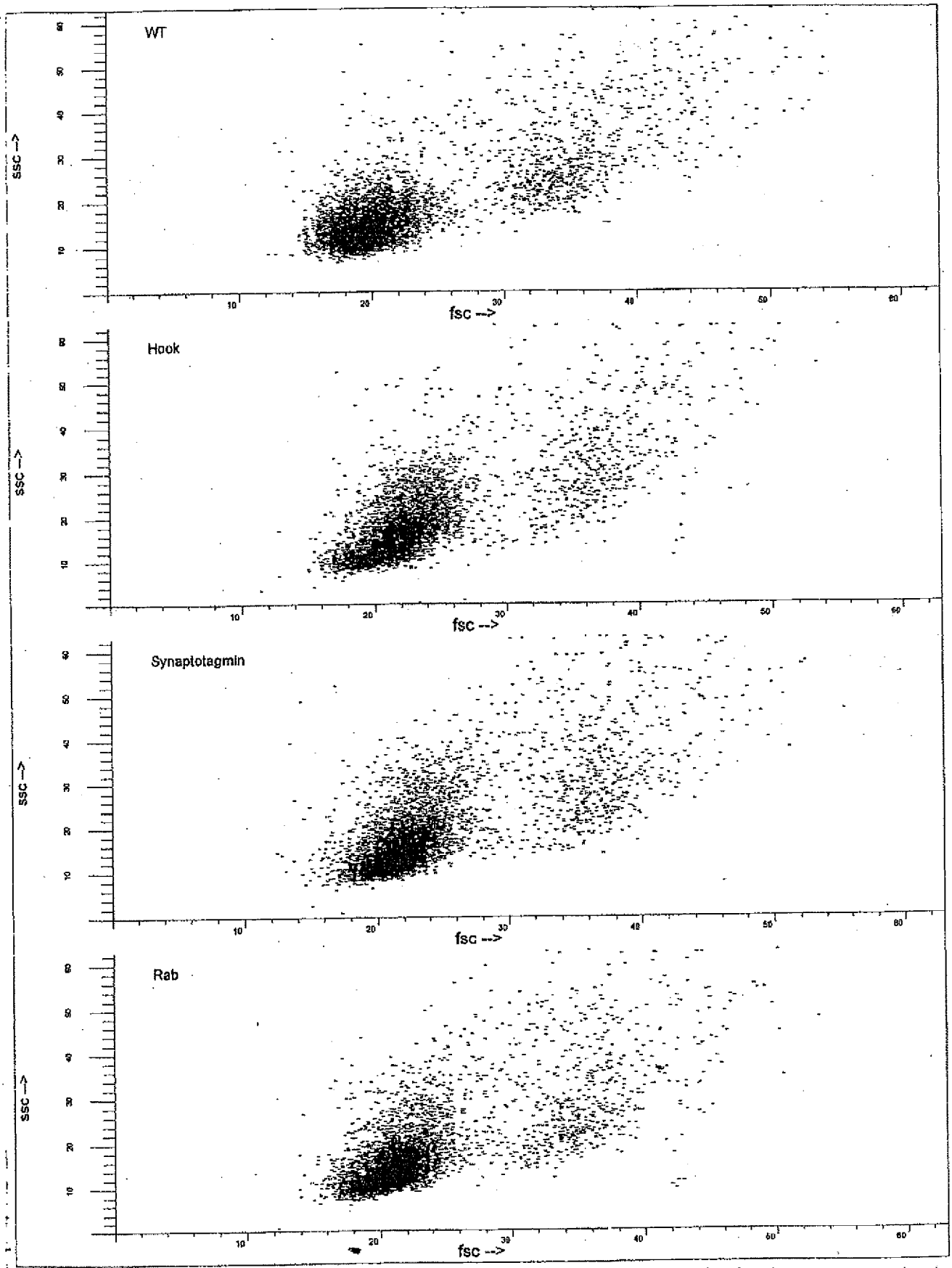
- Aspirate 2ml Cells, Take up in .3ml MT
  100Ω/Tube
  ⇒ one gets FM143 1μM
  " " " " + 2μM Ionomycin } 37°C ⇒ 30'
  " " PI

Via in FACSCAN

| | | | |
|---|---|---|---|
| - 001 | WT | 5 - | WT |
| - 2 | Hook | 6 + | WT |
| - 3 | Synaptotagmin | 7 - | Hook |
| - 4 | RAB | 8 + | " |
| | | 9 - | Synaptotagmin |
| | | 10 + | " |
| | | 11 - | RAB |
| | | 12 + | " |



| tnessed & Understood by me, | Date | Invented by | Date |
|---|---|---|---|
| | 8/23/97 | | 8/23/97 |

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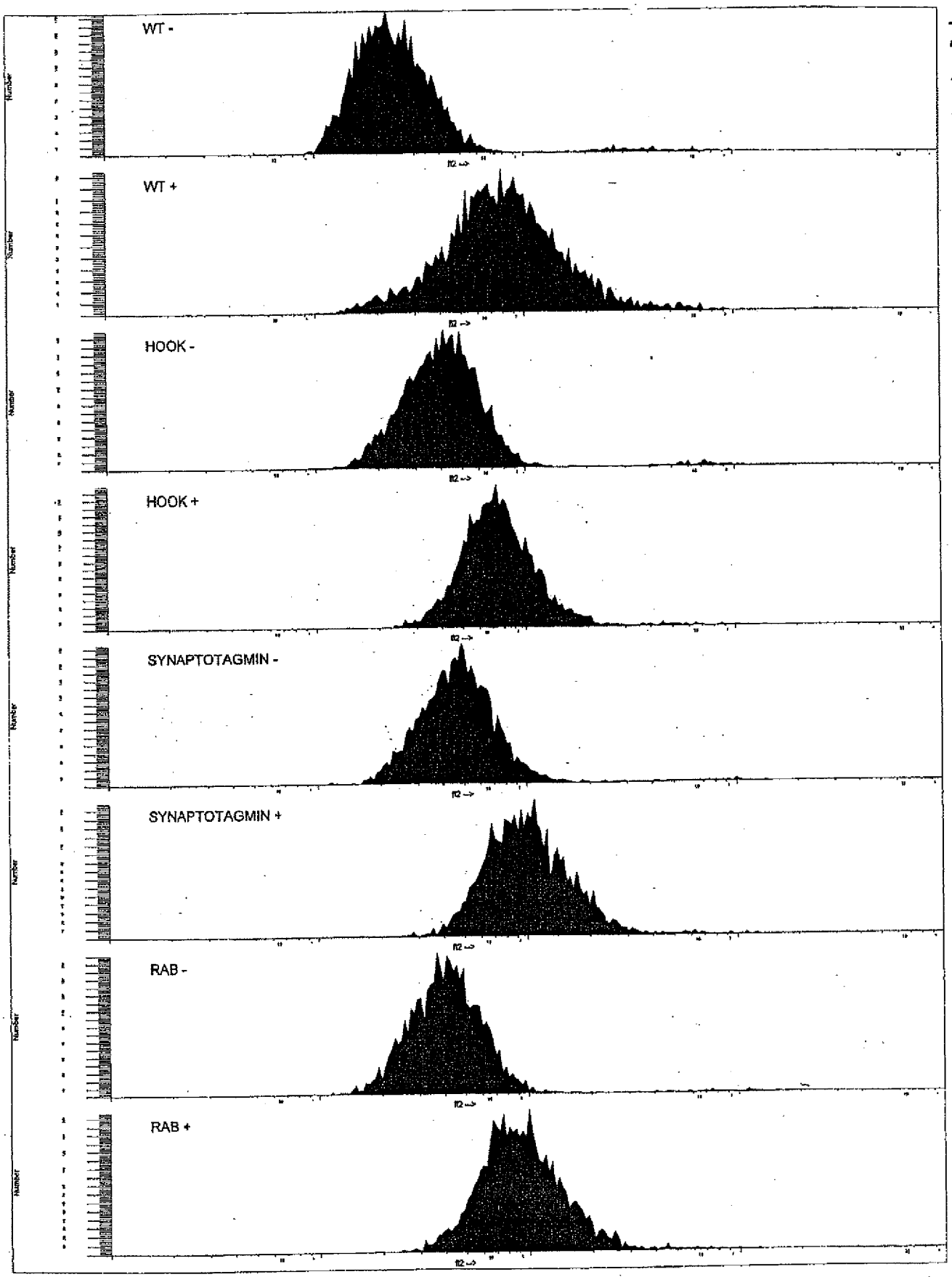
8/28

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8/25

= MC9 Cell Infection (Cont)

- Wells 3/4 + 6 of Transfections Look Significantly Brighter for GFP Than they did on 8/23
- ~1PM - Remove Viral Supe + Spin at 2500 RPM x 15' RT
- MC9 Cells, ~ $2.5 \times 10^6$/ml
- Spin Down 2ml x 6 MC9 Cells (~ $5 \times 10^6$/Tube)
- Add Viral Supes
- Divide Each into 2 Wells of a 6 Well Plate (~2ml / $2.5 \times 10^6$ Cells/Well)
  Add 4λ of 5mg/ml Polybrene Sulfate / Well SO FC = 10μg/ml
- Seal Plates and Spin for 90' at 2500 RPM
- Culture Ovn at 37°C (~ 3:30 PM →  )

- MC9 Cell Harvest - For Future cDNA Library Construction

Cells ~ $2 \times 10^6$/ml
- Spin down 200ml Cells
Wash 2x in Cold PBS / Aspirate
- Freeze on Dry Ice - 2 tubes x $2 \times 10^5$ Cells/Tube
- Store at -80°C



| Witnessed & Understood by me, | Date | Invented by | Date |
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| | | Recorded by | 8/25/97 |

8/24/17

MC9 Infections (Cont.)

2x 6 well Plates infected Yesterday

- ~ 11AM, Take Cells out of Wells/Pool, Wash Cells w/ 2ml MC9 Media, Spin, Decant
- Take up Pellets 1→6 with 12ml MC9 Media and Plate in T-75s

⇒ Quick Look at #6 Showed some GFP ⊕ Cells.

ires GFP Library Inf. Transfection

- Susan Plated 20 60 mm Plates of ΦE Cells Yesterday, today ~ 40% Confluent
- Randy Supplied DNA 10-62 Library - 14mer, ires GFP 850 ng/ml
- For Each 60mm Plate add (Plates have 6ml of Media)

8λ Chloroquine (50mM)
10Mg DNA (11.8λ)
122λ $CaCl_2$
876λ $H_2O$
1ml 2x HBS

Follow Standard Procedure

Transfected 17 Plates from 11:30AM → ~12:30AM

~ 6:30PM

- Aspirate Media
- Wash Cells 1x in PBS + Ca++
- Add Warm MC9 Media - 8ml/Plate Flask

⇒ 37°C ~ 7PM

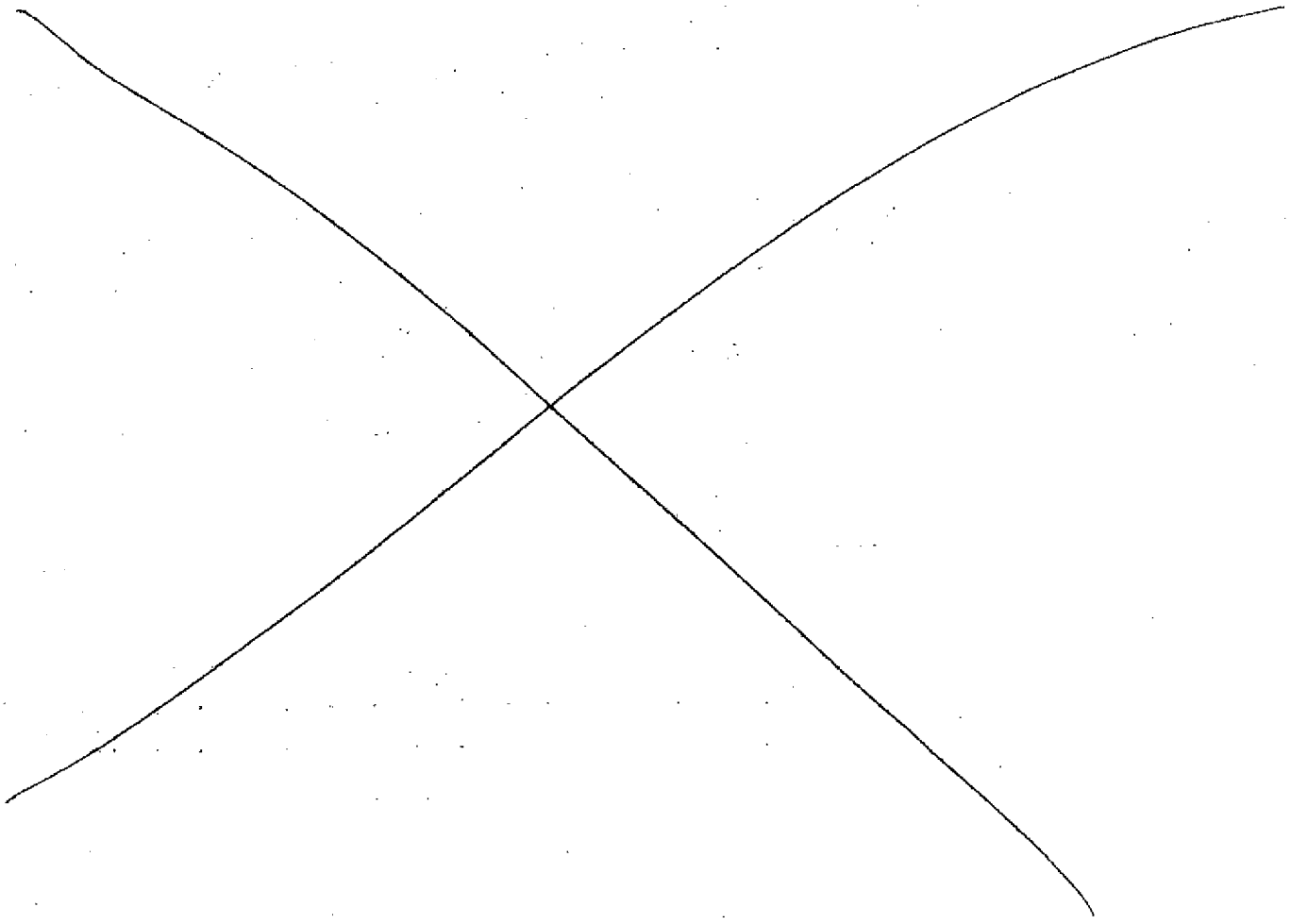


Witnessed & Understood by me. Date 8/24/17 Invented by [signature] Date 8/24/17

CEM - Library Infection

Library in iresGFP, ~$10^6$ Complexity of random 14-mer Peptides - Part of 2nd IgE Screen Library.

- Yesterday Susan S. Put CEM Media on Library Infected QA cells (After She Harvested her virus ~3PM) - Today Renae Spins (~4PM) Spin at 2500 RPM x10' Add PS to 10µg/ml
- CEM Cells ~1.1x$10^6$/ml
  Spin Down 60ml (~ 6.6x$10^7$ Cells Total)
  - Divide Pellets into 8 x12ml Spins ⇒ / 8x T-75s ⇒ 8.25x$10^6$ Cells/Flask
    Spin T-75s at 2500 RPM
    4:45 → 6:15
    Take out and Put at 37°C ON





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8/27/96

<ΦE Library Transfection>

A few GFP⊕ Cells Seen Today, but a minority.

~4PM Transfer Cells to 32°C

- Split MC9 Cells for tomorrow's Infection

[CEM Cells - Library Infection]

~1PM (22 hrs Post Infection Spin) Spin All infected CEM Cells - Decant Super
Take up in 90ml Fresh Media
Plate in 3x T-150's

- Take out 1ml of Library Infection, 1ml of WT Cells
Annexin-PE / PI Stain as done on 8/13 (use those Controls As Well)
View in FACSCAN

Files 001 WT
002 Library Infected

→ See next page

Save GFP⊕ Cells Staining up in Library Infected Afte 22 hrs

[Make MC9 Media]

DMEM (has Pyruvate and Glutamine)
18mg/500ml Asparagine
1x Non-essential AA
0.05mM 2-ME
PenStrep 1x
10% HI FBS
10% T-Stim Conditioned Media

.2um Sterile Filter



nessed & Understood by me, | Date 8/27/97 | Invented by | Date 8/27/97

9/8/97

EXHIBIT C

## CEM - Library Infected - Apoptosis Induction

XX gave me Library Infected Cells to test DNA Rescue Methods - CEM ~ $2.4 \times 10^6$/ml
Take 8ml ($2 \times 10^7$ Cells) + 4ml Fresh Media, Bring to 1uM Staurosporine
→ 37°C 10AM → 4PM (6 Hrs)
→ Annexin PE Stain as usual Procedure = files

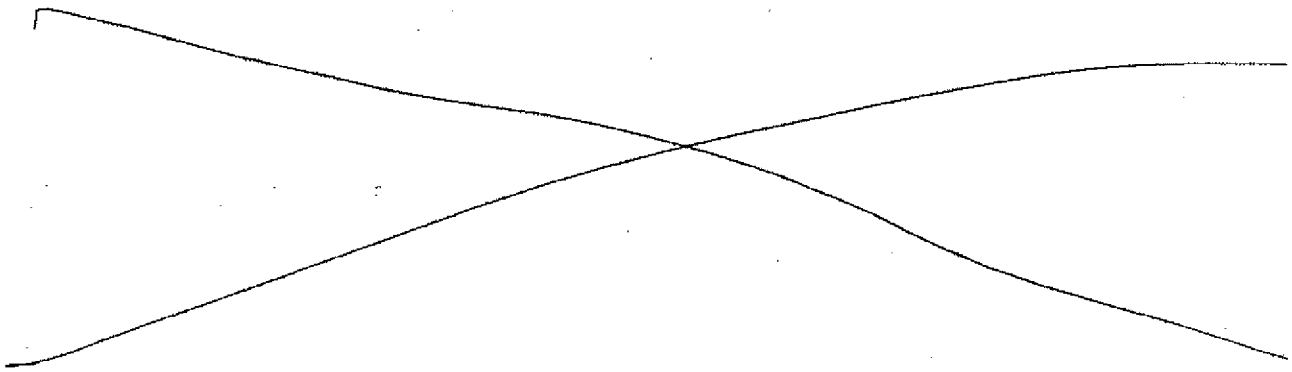
.015 GFP ONLY
16 Annexin PE ONLY
17 PI ONLY
18 GFP Library - Ø Stavo
19 " " + Stavo 7hrs
} No Settings

## CEM - Library - Staurosporine treatment 2x (9/3) - Nav 5 days post treatment

Take .5ml of Culture - Add PI
- FACSCAN - .001 - Library untreated
.002 Treated Stavo 2x

## MC9 Library - GFP Enriched

- GFP Enriched Cells from Last week - nav ~ $2.8 \times 10^6$/ml x 100ml
- Split Back to ~ $10^6$/ml for Tomorrow's Sort
- Remainder of Cells, ~ $2 \times 10^8$ Cells
Spin / Decant, Freeze in 5 vials ($4 \times 10^7$/vial) at -80°C)





| Witnessed & Understood By me | Date | Invented by | Date |
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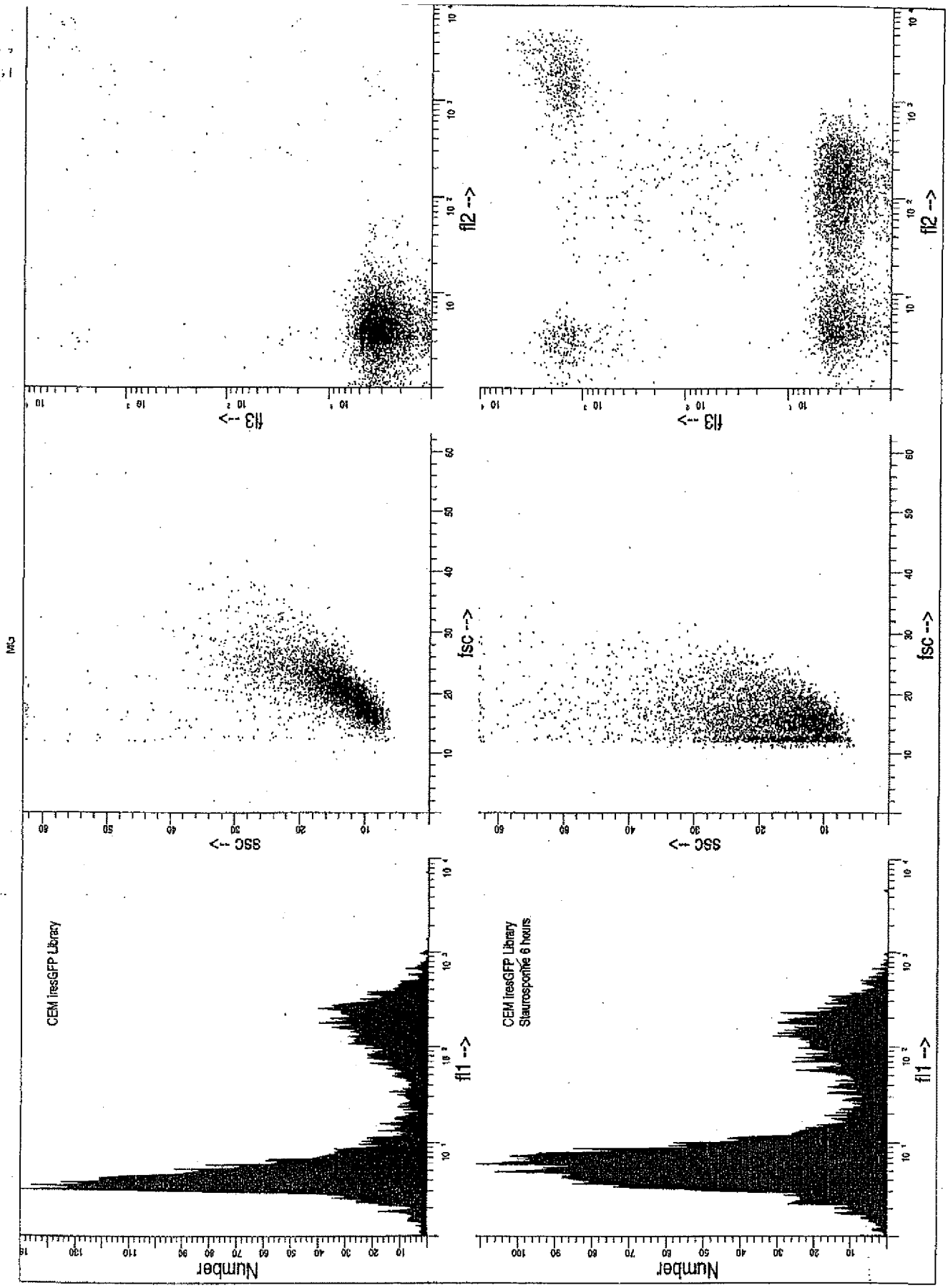


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## RELATED PROCEEDINGS APPENDIX

The instant application was appealed in 2008. Appeal No. 2009-015210 is relevant to this case. The Appeal Decision in Appeal No. 2009-015210 is submitted herewith.

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/293,670 | 04/16/1999 | JOSEPH FISHER | RIGL-036CIP | 5176 |

83092 7590 07/21/2010

Rigel Pharmaceuticals, Inc.
Bozicevic, Field & Francis LLP
1900 University Ave, Suite 200
East Palo Alto, CA 94303



| EXAMINER | |
|---|---|
| WESSENDORF, TERESA D | |
| ART UNIT | PAPER NUMBER |
| 1639 | |
| MAIL DATE | DELIVERY MODE |
| 07/21/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* JOSEPH FISHER, JAMES LORENS,
DONALD PAYAN, and ALEXANDER ROSSI

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Appeal 2009-015210
Application 09/293,670
Technology Center 1600

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Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This appeal under 35 U.S.C. § 134 involves claims to methods of screening cells. The Examiner rejected the claims as obvious.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## STATEMENT OF THE CASE

Claims 17-26, 30, and 32 stand rejected and are on appeal (App. Br. 3).[2] Claim 17, the only independent claim, is representative and reads as follows:

> 17. A method of screening for an alteration in cellular phenotype, said method comprising:
>
> a) providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents;
>
> b) sorting said population of cells based on at least five parameters using fluorescence activated cell sorting (FACS); and
>
> c) detecting at least one cell of said population having said alteration in said cellular phenotype;
>
> wherein said cellular phenotype is selected from a group of cellular phenotypes consisting of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a receptor protein.

The Examiner cites the following documents as evidence of unpatentability:

| | | |
|---|---|---|
| Uhr | US 5,612,185 | Mar. 18, 1997 |
| Nolan | WO 97/27212 | Jul. 31, 1997 |

Tao Jia-ping et al., *Multi-parameter sorting technique in flow cytometry*, 17 CHINESE JOURNAL OF PHYSICAL MEDICINE 168-171 (1995).

E. Conneally et al., *Rapid and Efficient Selection of Human Hematopoietic Cells Expressing Murine Heat-Stable Antigen as an Indicator of Retroviral-Mediated Gene Transfer*, 87 BLOOD 456-464 (1996).

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[2] Appeal Brief filed May 7, 2008.

Izumi Hide et al., *Degranulation of Individual Mast Cells in Response to $Ca^{2+}$ and Guanine Nucleotides: An All-or-None Event*, 123 THE JOURNAL OF CELL BIOLOGY 585-593 (1993).

The following rejections are before us for review:

(1) Claims 17-24 and 30, rejected under 35 U.S.C. § 103(a) as obvious over Uhr and Conneally (Ans. 4-7);

(2) Claims 17-25, 30, and 32, rejected under 35 U.S.C. § 103(a) as obvious over Nolan, Jia-ping, and Uhr (Ans. 7-10); and

(3) Claim 26, rejected under 35 U.S.C. § 103(a) as being unpatentable over Nolan, Jia-ping, Uhr, Hide, and Appellants' admitted prior art (Ans. 10-11).

OBVIOUSNESS -- UHR AND CONNEALLY

*ISSUE*

The Examiner finds that "Uhr, alone, discloses or teaches all the elements of the claim[ed] method. Uhr does not positively teach [a] library of retroviral vectors albeit, at least suggests said library of retroviral vectors" (Ans. 6).

To supplement the asserted suggestion in Uhr of using a library of retroviral vectors, however, the Examiner cites Conneally as teaching "the advantages in the use of recombinant retroviuses [sic] for the genetic modification of cells," the advantages including "the ability to assess gene transfer to specific subpopulations of cells immediately after infection. The detectable level is sorted by FACS" (*id.* at 6-7).

Based on these advantages, the Examiner concludes that the "use of recombinant retroviral vectors to transfect cells would have been obvious to

one having ordinary skill in the art at the time the invention was made as taught by Conneally and at least contemplated by Uhr" (*id.* at 7).

"In a nutshell, the Appellants submit that the claims are not obvious in view of the cited references because neither of the cited references provide a library of retroviral vectors" (App. Br. 5). Specifically, Appellants argue, the portion of Uhr cited by the Examiner to meet that feature, column 22, lines 14-20, only teaches inducing cell cycle arrest in tumor cells using gene therapy (*id.* at 6), and Conneally fails to remedy that shortcoming (*id.* at 7).

The Examiner responds that column 22 of Uhr teaches that the gene therapy may be effected using retroviruses (Ans. 11), and also teaches that cells may be transfected with at least two genes, c-fos and c-jun (*id.* at 13). Thus, the Examiner reasons, because the Specification defines "'library of cells'" as meaning "at least two cells", the claims encompass the process suggested by Uhr (*id.* at 13-14).

In view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether the evidence of record supports the Examiner's finding that the cited references suggest a process that includes a step of "providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents" as recited in claim 17.

*FINDINGS OF FACT ("FF")*

*Claims and Specification*

1. Claim 17 recites a method of screening for an alteration in cellular phenotype. The method's first step is "(a) providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents."

2. The Specification states that, "[b]y a 'population of cells' or 'library of cells' or 'plurality of cells' herein is meant at least two cells, with at least about $10^3$ being preferred, at least about $10^6$ being particularly preferred, and at least about $10^8$ to $10^9$ being especially preferred" (Spec. 9).[3]

*The Prior Art*

3. Uhr discloses "strategies for the treatment of cancer, including methods to induce or maintain a state of arrest to prevent tumor growth or metastasis" (Uhr, col. 2, ll. 62-65).

4. In one embodiment Uhr discloses that "it is contemplated that tumor cell cycle arrest may be induced by gene therapy. DNA encoding key genes in this process, such as, for example, c-fos or c-jun, may be applied directly to cells, in the form of oligonucleotides, or other genetic constructs" (*id.* at col. 22, ll. 6-10).

5. Uhr further discloses that the "preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes, once introduced into the cells to be treated, is also contemplated. In this regard, replication defective retrovirus, such as LNSX, LN or N2A, may be used" (*id.* at col. 22, ll. 14-19).

6. Uhr further discloses that "[s]everal studies are contemplated to assay the effects of fos expression, and a variety of other protooncogenes, on malignant growth and cell cycle arrest, both in in vivo and in vitro" (*id.* at col. 22, ll. 43-45).

7. Uhr discloses, for example, that "[t]ransfected clones will be introduced into normal Balb/c and Id-immune mice, in controlled

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[3] Substitute Specification filed June 3, 2002.

experiments, and malignant growth [will] be evaluated" (*id.* at col. 22, ll. 48-50).

8. Uhr discloses that "it will be important to demonstrate the presence of cell cycle arrested tumor cells. Spleen from mice >60 days after tumor cell transplant will be analyzed for arrested $BCL_1$ cells by FACS, employing the methods of the present invention" (*id.* at col. 22, ll. 56-60).

9. Uhr discloses that, using its FACS cell sorting methods, "cells can be sperated [sic] on the basis of 6 parameters" (*id.* at col 3, ll. 64-65).

10. Conneally discloses studies of retroviral transfection of "primary human hematopoietic cell targets using an amphotropic vector encoding heat-stable antigen (HSA) . . . as a selectable marker" (Conneally 457).

11. Conneally discloses:

> These studies highlight the potential of using retroviral constructs encoding cell surface markers not normally expressed on the target cells of interest to facilitate the selection immediately after infection of those to which gene transfer has been achieved. For many gene therapy applications, the capacity to control the number or proportion of transduced stem cells could be of considerable significance . . . .

(Conneally 462.)

12. Thus, Conneally discloses, "[o]ne of the major advantages of the HSA/CD24 family of vectors is the ability to assess gene transfer to specific subpopulations of cells immediately after infection" (*id.*)

*PRINCIPLES OF LAW*

In *KSR Int' l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court advised that, in determining whether the prior art supplied a reason for practicing the claimed subject matter, the analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for

a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.").

The Court also reasoned that "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* at 419.

Lastly, during examination, the PTO must interpret terms in a claim using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

*ANALYSIS*

We agree with the Examiner that the evidence of record supports a finding that the cited references suggest a process that includes a step of "providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents" as recited in claim 17.

The Specification defines a "population of cells" or "library of cells" or "plurality of cells" as meaning "at least two cells" (Spec. 9 (FF 2)). Given this definition, we further agree with the Examiner that the population of retroviral-transfected cells suggested by Uhr, which would include at least two retroviral vectors (one encoding c-fos, the other encoding c-jun), would

be encompassed by the "population of cells comprising a library of retroviral vectors" recited in claim 17.

Turning to the prior art, Uhr discloses processes of treating cancer by arresting tumor cells' growth cycle (FF 3-4). Uhr discloses that cell cycle-arresting genes, such as c-fos and c-jun can be introduced into cells using retroviruses (FF 4-5). Uhr further discloses that the effect of the genes encoded by the retroviruses can be studied by implanting the gene-carrying cells into mice, and then removing presumed cycle-arrested cells from the mice and sorting them by FACS, using as many as 6 parameters, to evaluate the presence of the altered cell cycle phenotype (FF 6-9).

In view of these teachings, we agree with the Examiner that Uhr would have suggested to an ordinary artisan that it would be desirable to transfect a population of cells with retroviral vectors encoding at least two potential cell cycle-arresting genes, c-fos and c-jun. As pointed out by the Examiner, Conneally also discloses the desirability of using retroviral vectors having detectable cell surface markers as vehicles for nucleic acids of interest (FF 10-12).

We acknowledge, as Appellants argue, that Uhr refers to its methods as "gene therapy" (FF 4). Regardless of terminology, however, given Uhr's teachings, we find that Uhr would have prompted an ordinary artisan to provide a population of cells including at least two different retroviral vectors encoding tumor cell cycle-arresting agents, one encoding c-fos, the other encoding c-jun.

In sum, we agree with the Examiner that an ordinary artisan viewing the teachings of the cited references have been prompted to transfect a population of cells with retroviral vectors encoding at least two potential cell

cycle-arresting genes, c-fos and c-jun. As claim 17 encompasses a library of this size, we conclude that the evidence of record supports the Examiner's position that the cited references suggest performing claim 17's step of "providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents."

Accordingly, we affirm the Examiner's obviousness rejection of claim 17 over Uhr and Conneally, as well as the rejection of claims 18-24 and 30, which were not argued separately. *See* 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS -- NOLAN, JAI-PING AND UHR

*ISSUE*

Claims 17-25, 30, and 32 stand rejected under 35 U.S.C. § 103(a) as obvious over Nolan, Jia-ping, and Uhr (Ans. 7-10).

In traversing this rejection, Appellants do not dispute the Examiner's fact findings regarding the references' teachings or the conclusions drawn from them. Rather, Appellants argue only that the Nolan reference is not prior art with respect to the instant application as evidenced by the Fisher Declaration (App. Br. 7-9).

Specifically, Appellants argue, the instant application claims priority to an application (09/062,330) filed less than one year after the publication date of the Nolan reference, and the Nolan reference is therefore available as prior art to the instant application only under 35 U.S.C. § 102(a) (*id.* at 8). Thus, Appellants urge, because the Fisher Declaration filed under 37 C.F.R. § 1.131 establishes invention of the subject matter in the rejected claims prior to the publication date of Nolan, Nolan is not available as prior art against the rejected claims (*id.*). Appellants further urge that the Examiner has failed to properly consider the Fisher Declaration (*id.*)

The Examiner responds that "Nolan was published more than one year [before] applicants' earliest filing date (please note appellants' statement that the instant application is a continuation-in-part (CIP) of the 09/062,330 application)" (Ans. 17). *See also* Final Rejection 13 (entered August 10, 2007) ("[T]he 35 USC 1.131 declaration does not overcome the 103 rejection *based on 102(b)* rejection over the Nolan reference as Nolan (WO 97/27212) *is a bar* against the instant application.") (Emphasis added).

Specifically, the Examiner urges, Appellants "are not entitled to the priority date of the '330 application" because the '330 application does not provide support for screening for "'at least five parameters,'" and also does not provide support for screening for all of the phenotypes recited in the rejected claims (Ans. 17).

In view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether Appellants are entitled to priority to parent application serial no 09/062,330, which issued as U.S. Patent 6,897,031.

*PRINCIPLES OF LAW*

37 C.F.R. § 1.131 states, in relevant part (emphasis added):

> (a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. . . . Prior invention *may not be established* under this section if . . .
>
> (2) The rejection is based on a statutory bar.

Thus, a declaration under 37 C.F.R. § 1.131 cannot overcome a rejection for anticipation or obviousness where the prior art antedates the application's effective filing date by more than one year, and is therefore applicable against the claims under 35 U.S.C. § 102(b). *See In re Foster*, 343 F.2d 980, 989-90 (CCPA 1965).

Accordingly, for Appellants to overcome the statutory bar set by § 102(b), Appellants' claimed subject matter must find support in Application Serial No. 09/062,330, filed on April 17, 1998, which issued as U.S. Patent No. 6,897,031 B1 (*see* FF 16, *below*).

"[T]he test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application." *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004).

Thus, to receive benefit of a previous application, *every feature* recited in the claims at issue must be described in the prior application. *See In re van Langenhoven*, 173 USPQ 426, 429 (CCPA 1972) ("The fact that *some* of the elements of the breech claims have support of the parent and foreign applications does not change the result. *As to given claimed subject matter, only one effective date is applicable.*") (Emphasis added); *accord In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995).

*FINDINGS OF FACT ("FF")*

13. It is undisputed that the publication date of the Nolan reference is July 31, 1997.

14. The filing date of the instant application is April 16, 1999 (*see* Transmittal of New Application (entered April 16, 1999)), which is more than one year after the publication date of the Nolan reference.

15. The Specification states that "[t]his application is a continuation-in-part of U.S. Application Serial No. 09/062,330, filed on April 17, 1998 [now U.S. Patent No. 6,897,031 B1], and U.S. Application Serial No. 09/157,748, filed on September 21, 1998 (Specification 1 (as amended September 24, 2004)).

16. Thus, to remove the statutory bar set by 35 U.S.C. § 102(b) against patenting claims anticipated or obviated by printed publications available more than one year prior to an application's filing date, Appellants' claimed subject matter must find support in Application Serial No. 09/062,330, filed on April 17, 1998, which issued as U.S. Patent No. 6,897,031 B1.

17. The Examiner finds:

> The 09/062330 (now US Patent 6,897,031) ('031 Patent) does not provide support for the present broad claim "at least 5 parameters" as applied to the different claim cellular phenotypes. The different claim phenotypes consist of cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a receptor protein. The '031 Patent provides only four (4) parameters solely for exocytosis. It does not provide support for the other claim cell phenotypes having "at least five (5)" parameters being determined. See e.g., Example 9 of the '031 Patent.

(Ans. 17.)

18. Appellants do not dispute the Examiner's characterization of the disclosure of the '330 application/'031 patent.

19. The '031 patent states:

> Described is a method for screening for alterations in exocytosis of a population of cells. The cells are sorted by a FACS machine by assaying for alterations in at least three of the properties selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins. Methods for screening for bioactive agents capable of modulating exocytosis in a cell are also described. The methods provide for reduced background and increased specificity without increasing the time or steps involved in assaying for exocytosis.

('031 patent, abstract).

20. Appellants do not point to any disclosure in the '031 patent regarding sorting cells based on at least five parameters as recited in step (b) of claim 17. Nor do Appellants point to any disclosure of screening for alterations in all of the cellular phenotypes recited in the "wherein" clause of claim 17.

*ANALYSIS*

We agree with the Examiner that Appellants have not shown that the Nolan reference is unavailable as prior art against the rejected claims. As noted above, Appellants cannot avail themselves of an antedating declaration under 37 C.F.R. § 1.131 if the rejection is a statutory bar. *See In re Foster*, 343 F.2d at 989-90.

Thus, to avoid the statutory bar set by 35 U.S.C. § 102(b), Appellants must find descriptive support for the rejected claims in a priority application filed less than one year after publication of the Nolan reference. In the instant case, only the '330 application, which issued as the '031 patent, and which is asserted as a continuation-in-part parent to this application, has such a filing date (*see* FF 15).

However, as the Examiner points out, and Appellants do not dispute, the '330 application/'031 patent does not describe all of the features in the rejected claims (FF 17-20). Thus, given the evidence of record, the earliest effective filing date of the instant application is April 16, 1999, which is more than one year after the Nolan reference's publication date of July 31, 1997 (FF 13-14). Accordingly, the Fisher Declaration under 37 C.F.R. § 1.131 cannot be used to antedate the Nolan reference.

We therefore agree with the Examiner that Nolan is available prior art against the rejected claims. As Appellants' sole argument was on this basis, and as we detect no other deficiency in the Examiner's case of obviousness, we affirm the Examiner's obviousness rejection of claims 17-25, 30, and 32 over Nolan, Jia-ping, and Uhr.

The Examiner also rejected claim 26 as obvious over Nolan, Jia-ping, Uhr, Hide, and Appellants' admitted prior art (Ans. 10-11). Appellants' sole argument against this rejection is also the unavailability of Nolan as prior art against the rejected claim (App. Br. 9). As discussed above, we do not find this argument persuasive. We therefore also affirm this rejection.

## SUMMARY

We affirm the Examiner's obviousness rejection of claims 17-24 and 30 over Uhr and Conneally.

We also affirm the Examiner's obviousness rejection of claims 17-25, 30, and 32, over Nolan, Jia-ping, and Uhr.

We also affirm the Examiner's obviousness rejection of claim 26 over Nolan, Jia-ping, Uhr, Hide, and Appellants' admitted prior art.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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RIGEL PHARMACEUTICALS, INC.
BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVE, SUITE 200
EAST PALO ALTO, CA 94303